Blood pressure variability

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Objectives

• To describe the different types of blood pressure variability (BPV)

• To explain the causes and significance of BPV

The content is aimed at healthcare professionals working in primary care, or those in training
Contents

• Different types of blood pressure variability (BPV) and their significance
• How to measure BPV
• Determinants of different types of BPV
• Consequences of short-term (24-hour) BPV
• Consequences of longer-term BPV
• Effects of different antihypertensive agents on BPV

Slide notes are included on several slides
Slide notes also contain source materials and references
Blood pressure variability (BPV)

- Blood pressure (BP) normally fluctuates throughout the day, from day to day and over more prolonged periods of time, related to:
  - Internal factors, such as stress and emotion
  - External factors, such as environmental changes
- Ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM) can detect some types of BPV and the morning BP surge
- Guidelines recommend using ABPM or HBPM to help diagnose and manage hypertension
- Differences between ABPM or HBPM values and office/clinic BP can identify white-coat hypertension or masked hypertension
- During sleep, BP is normally reduced by 10–20% of daytime values – “dipping”. Reduced nocturnal dipping is associated with increased cardiovascular risk


Slide notes:
Cut-off values for the definition of hypertension are systolic blood pressure (SBP) $\geq 135$ and/or diastolic blood pressure (DBP) $\geq 85$ mmHg for home blood pressure monitoring (HBPM) and daytime ambulatory blood pressure monitoring (ABPM), and SBP $\geq 130$ and/or DBP $\geq 80$ mmHg for 24-hour ABPM, according to the 2013 European Society of Hypertension (ESH)/European Society of Cardiology (ESC) Guidelines.\(^1\)

Subjects with masked hypertension have office SBP $< 140$ and DBP $< 90$ mmHg but a raised out-of-office BP and have a cardiovascular (CV) risk in the office hypertension range. Subjects with white-coat hypertension have office SBP $\geq 140$ and/or DBP $\geq 90$ mmHg but normal out-of-office BP and have lower CV risk than for the same office BP with raised out-of-office BP.\(^1\)

Sometimes the ‘white-coat effect’ is defined as a discrepancy of more than 20/10 mmHg between clinic and average daytime ABPM or average HBPM values.\(^2\)

In a meta-analysis of CV events in white-coat, masked and sustained hypertension versus true normotension, the adjusted hazard ratio (HR) versus normotension for CV events was 1.12 (95% confidence interval [CI] 0.84-1.50, $P=0.59$) for white-coat hypertension, 2.00 (1.58-2.52, $P<0.001$) for masked hypertension, and 2.28 (1.87-2.78, $P<0.001$) for sustained hypertension. This indicates that the incidence of CV events is not significantly different between patients with white-coat hypertension and those with true normotension, whereas the outcome is worse in patients with masked or sustained hypertension.\(^3\)

References:
Slide notes:
Rather than a general steady value, there are marked short-term and long-term fluctuations in blood pressure values resulting from complex interactions between environmental and behavioural factors and cardiovascular regulatory mechanisms. As well as absolute blood pressure values, adverse cardiovascular events are associated with blood pressure variability (BPV). Increased short-term and long-term BPV is associated with cardiac, vascular and renal damage and with an increased risk of cardiovascular events and mortality. Within-patient visit-to-visit BPV is strongly prognostic for cardiovascular morbidity and mortality.
Assessment within a treatment group

Within-individual variability: multiple readings within each subject available

Inter/between-individual variability: single readings for each subject available.

Reference:
BPV comparisons used for statistical analysis

- The standard deviation (SD) of the differences of individual BP measurements from the sample mean and coefficient of variation (CV) of BP measurements are commonly used parameters to evaluate BPV in clinical trials.

<table>
<thead>
<tr>
<th>BPV indices</th>
<th>Formula/derivation</th>
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<tbody>
<tr>
<td>SD</td>
<td>$SD = \sqrt{\frac{\sum(\text{individual readings} - \text{sample mean})^2}{n}}$</td>
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<tr>
<td>CV</td>
<td>$CV = \frac{SD}{\text{mean}}$</td>
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Slide notes:
In clinical trials, blood pressure variability is measured using either the standard deviation of the differences between individual blood pressure measurements and the sample mean, or the coefficient of variation of the blood pressure measurements.
Slide notes:
This slide provides details of the different factors that play a role in short- and longer-term blood pressure variability. These factors are important as there is increasing evidence that blood pressure medication should strive to produce a consistent blood pressure over time as well as blood pressure lowering, to be maximally cardioprotective.

Reference:
Increased 24-hour BPV has been associated with cardiovascular damage

• In patients with mild-to-moderate hypertension, 24-hour BPV has been related to the rate and severity of target-organ damage assessed by presence of:
  – Left ventricular hypertrophy +/- strain
  – Cardiac enlargement
  – Cardiac volume
  – Ocular fundus
  – Ischaemic heart disease
  – Heart failure
  – Cerebrovascular insufficiency
  – Peripheral vascular disease
  – ECG abnormalities
  – Abnormalities in renal function

ECG, electrocardiogram.

Reference:

Slide notes:
In 108 hospitalised subjects with essential hypertension, intra-arterial 24-hour blood pressure (BP) was recorded. For nearly any level of 24-hour mean BP, subjects with low 24-hour BPV had a lower prevalence and severity of target-organ damage than those with high 24-hour BPV (*P*<0.05).\(^1\)

Reference:
Blood pressure variability (BPV) was assessed as the standard deviation of the mean out of 24-hour, awake and asleep ambulatory BP recordings in 180 untreated subjects. Increased awake systolic BPV over a 24-hour period correlated with subclinical target-organ damage:

- Carotid intima-media thickness (IMT) and left ventricular mass index (LVMI) progressively increased across tertiles of awake systolic BPV over a 24-hour period (180 patients, $P$ for trend 0.001 and 0.003, respectively)
- Awake systolic BPV was identified as an independent predictor for these endpoints.

Reference:
Excessive circadian BPV

- Prospective, 6-year study of 297 Japanese subjects, 48-hour ABPM at baseline
- Excessive circadian blood pressure amplitude (BP-A) at baseline was associated with a relative risk of
  - Ischaemic stroke 8.2 (95% confidence interval [CI] 3.1–21.7; \( P < 0.001 \))
  - Nephropathy 6.9 (95% CI 2.9–16.3; \( P < 0.001 \))
- Further analysis showed the excessive circadian BP-A or Circadian Hyper-Amplitude-Tension (CHAT) was associated with a higher relative risk for ischaemic stroke and nephropathy than all other conventional risk factors
- Decreased heart rate variability (DHRV) was another risk factor
- Treatment should be optimised by timing its administration (chronotherapy) and selecting a treatment schedule best suited to normalise abnormal patterns in BP and/or heart rate

References:

Slide notes:
In a prospective study of 297 Japanese subjects over 6 years, excessive circadian blood pressure amplitude (BP-A) at baseline was associated with a relative risk of 8.2 (95% CI 3.1-21.7; \( P < 0.001 \)) for ischaemic stroke and 6.9 (2.9-16.3; \( P < 0.001 \)) for nephropathy.\(^1\)

Subsequent analysis by Cornelissen and colleagues showed the excessive circadian BP-A or Circadian Hyper-Amplitude-Tension (CHAT) was associated with a higher relative risk for ischaemic stroke and nephropathy than all other conventional risk factors. Decreased heart rate variability (DHRV) was also identified as a risk factor and it was recommended that the efficacy of any treatment should be optimised by timing its administration (chronotherapy) and selecting a treatment schedule best suited to normalise abnormal patterns in blood pressure and/or heart rate.\(^2\)
In the PAMELA (Pressioni Arteriose Monitorate e Loro Associazioni) Study of long-term prognostic value of blood pressure variability (BPV) in the general population (2012 individuals randomly selected from the population of Monza, Milan), the adjusted (for age, sex, 24-hour mean blood pressure and other risk factors) risk of cardiovascular death was not related to the 24-hour, day, or night blood pressure standard deviations but was inversely related to day-night diastolic blood pressure difference (beta coefficient = -0.040; P<0.02) and showed a significant positive relationship with residual or erratic diastolic BPV (beta coefficient = 0.175; P<0.002) from Fourier spectral analysis. This showed that short-term erratic components of BPV play a prognostic role indicating cardiovascular risk.

Reference:
Slide notes:
In the Natrilix SR Versus Candesartan and Amlodipine in the Reduction of Systolic Blood Pressure in Hypertensive Patients (X-CELLENT) Study, 24-hour ambulatory blood pressure monitoring was carried out every 15 minutes over 24 hours. Increasing age, systolic blood pressure (SBP) and heart rate variability were major determinants of blood pressure variability (BPV). There were four parallel treatment arms (placebo, candesartan, indapamide sustained-release and amlodipine).¹
In the visit-to-visit BPV study from the Third National Health and Nutrition Examination Survey (n=956), measurements were over three visits over a median of 17 days. Increasing age, SBP and pulse pressure, female gender, a history of myocardial infarction and use of angiotensin converting enzyme inhibitors were associated with increased BPV. Higher levels of short-term visit-to-visit variability in SBP were associated with increased all-cause mortality.²

References:
The Natrilix SR Versus Candesartan and Amlodipine in the Reduction of Systolic Blood Pressure in Hypertensive Patients (X-CELLENT) trial was multicentre, multinational, randomised, double blind and placebo controlled. Patients were randomised to one of four parallel treatment arms – placebo, candesartan, indapamide sustained-release and amlodipine. Within-subject mean and standard deviation of 24-hour blood pressure, weighted by time interval between consecutive readings, were calculated in three time frames: daytime, night-time and 24 hours to evaluate blood pressure and blood pressure variability.

Reference:
Although there has been awareness of blood pressure variability (BPV), the importance of this variable to clinical outcomes has not, historically, been considered important. Evidence reviewed by the European Society of Hypertension (ESH)/European Society of Cardiology (ESC) for their guidelines published in 2013 was not conclusive as to the importance of BPV.

References:
Rothwell PM. *Lancet* 2010;375:938-948.
## Short-term BPV has been evaluated in several clinical trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Follow-up schedule</th>
<th>No. of measurements at each follow-up</th>
<th>BPV types</th>
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</thead>
<tbody>
<tr>
<td>X-CELLENT²</td>
<td>Baseline and week 12</td>
<td>24-hour ABPM (every 15 min readings)</td>
<td>Min-to-min</td>
</tr>
<tr>
<td>Ichihara, et al² (daytime)</td>
<td>Baseline and 12 months</td>
<td>24-hour ABPM (every 30 min for 16 hours)</td>
<td>Hour-to-hour</td>
</tr>
<tr>
<td>Ichihara, et al² (night-time)</td>
<td>Baseline and 12 months</td>
<td>24-hour ABPM (hourly at night for 8 hours)</td>
<td>Day-to-day</td>
</tr>
<tr>
<td>Ohasama study³</td>
<td>HBPM for 26 days</td>
<td>Once every morning</td>
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<tr>
<td>NHANES III⁴</td>
<td>Baseline, 1 month and second visit (mean = 17 days interval from 1-month visit)</td>
<td>Single reading</td>
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HBPM, home blood pressure measurement.


### Slide notes:
A number of clinical trials have incorporated blood pressure variability (BPV) measurements in their evaluation of drug efficacy. This reflects the growing evidence that BPV is important for cardiovascular morbidity.

### References:
Day-to-day BPV is an independent predictor of CV risk

- The Ohasama observational study of 2455 Japanese residents aged between 35 and 96 years concluded that day-to-day BPV is an independent predictor of CV and stroke mortality after adjustment for mean BP
- Home BP and heart rate were measured once every morning for 26 days

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Prognostic effect of increase in systolic BPV of +1 between-subject SD</td>
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<tr>
<td>CV mortality</td>
<td>1.27</td>
<td>0.002</td>
</tr>
<tr>
<td>Stroke mortality</td>
<td>1.41</td>
<td>0.0009</td>
</tr>
<tr>
<td>Cardiac mortality</td>
<td>1.13</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Adjusted for sex, age, obesity, smoking and drinking, history of CV disease, diabetes mellitus, hyperlipidaemia and treatment with antihypertensive drugs, systolic BP and HR

Reference:

Slide notes:
2455 residents of Ohasama, Japan (age range 35-96 years; 60.4% women) measured their blood pressure and heart rate each morning for a mean of 26 days. Participants were followed, and 462 deaths occurred over a median of 11.9 years, of which 168 were cardiovascular deaths (83 stroke, 85 cardiac).
An increase in blood pressure variability of +1 between-subject standard deviation was associated with increased hazard ratios for cardiovascular (1.27; P=0.002) and stroke mortality (1.41; P=0.0009), but not cardiac mortality.

Reference:
Slide notes:
Underlying usual blood pressure is the measure most often used to account for blood pressure-related risk of vascular events. Trials of antihypertensive medications are generally looking beyond simple blood pressure measurements, and are also monitoring blood pressure variability as a risk predictor of vascular events and as a monitor of the benefit of antihypertensive drugs on test.

References:
The relationship between risk of stroke and visit-to-visit variability in blood pressure (expressed as standard deviation) and maximum blood pressure was assessed in patients who had survived a previous transient ischaemic attack (TIA) in the UK-TIA trial and three validation cohorts, and in patients with treated hypertension in the Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure Lowering Arm (ASCOT-BPLA).

In each TIA cohort, visit-to-visit variability in systolic blood pressure (SBP) was a strong predictor of subsequent stroke, as was maximum SBP reached. In the ASCOT-BPLA analysis, the average blood pressure had a moderate effect on the risk of stroke and no effect on coronary events, but variability in SBP was found to be a strong predictor of stroke and coronary events in hypertensive patients, especially in younger patients.

Reference:
A study of treated hypertensive patients in the Glasgow Blood Pressure Clinic assessed blood pressure variability (BPV) by the average real variability (ARV) for systolic blood pressure and diastolic blood pressure calculated as the average absolute difference between successive blood pressure measurements taking the order of the blood pressure measurements into account. The figure shows the hazard ratios for all-cause mortality in four quartiles of systolic blood pressure variability in 2706 patients with moderate hypertension (systolic blood pressure, 140-160 mmHg) during the first year of treatment. Patients with the highest quartile of BPV had a 60% increased risk of all-cause mortality compared with those with lowest BPV.

Reference:
In this post-hoc analysis of the INVEST (International Verapamil SR–Trandolapril Study) trial in 22,576 patients with hypertension and coronary artery disease, consistency of blood pressure control was defined as the proportion of visits in which blood pressure was in control (<140/90 mm Hg), divided into 4 groups: <25%, 25% to <50%, 50% to <75% and ≥75%. The risk of the primary outcome (first occurrence of death, nonfatal myocardial infarction or nonfatal stroke) decreased progressively from the group with <25% to the group with ≥75% of visits with blood pressure control, as did the risk for myocardial infarction and stroke. This was independent of baseline blood pressure and mean on-treatment blood pressure.

Reference:
Blood pressure fluctuations occur and can be detected with various forms of monitoring. These fluctuations were thought to be “background noise” or to occur randomly, but have been shown to be the result of complex interactions between environmental and behavioural factors and intrinsic cardiovascular regulatory systems. Increased blood pressure fluctuation is associated with cardiac, vascular and renal damage.

Reference:
Slide notes:
This meta-analysis found that treatment with different classes of antihypertensive drugs affected systolic blood pressure variability – calcium channel blockers and non-loop diuretics reduced the variability, while other classes of antihypertensives increased the variability. This may account for differences in the risk of stroke with different antihypertensive agents.

Reference:
Compared with other drug classes, calcium channel blockers and non-loop diuretic drugs reduced inter-individual variation in systolic blood pressure, whereas angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and beta blockers increased it, with calcium channel blockers reducing inter-individual variation the most, versus placebo.

Across all trials in which data were reported, effects of treatment on inter-individual variation in systolic blood pressure were correlated with effects on risk of stroke independently of differences in mean systolic blood pressure. These drug-class effects are most probably explicable on the basis of effects on within-individual variability in systolic blood pressure.

Reference:
Evidence suggests that reducing BPV also prevents vascular outcomes

- How BP reduction is achieved and sustained is clinically important
- Reducing BP fluctuation over time as well as mean BP has recently been recognised as a potential target for improved management of hypertension to prevent vascular outcomes, particularly stroke.¹,²

Aim to reduce both BP and BPV

Conclusions

- Reducing BPV is a potential target for improved management of hypertension to prevent vascular outcomes, particularly stroke
- HBPM can help to identify increased BPV; ABPM is required to assess night-time BP
- Visit-to-visit BPV increases CV risk
- Smooth control of BP over 24 hours is desirable, including adequate dipping at night and reduction of the early-morning BP surge
- CCBs reduced BPV more than other antihypertensive drugs in some studies and longer-acting drugs may have an advantage in reducing BPV
- Visit-to-visit BP fluctuations may reflect poor drug adherence or inappropriate medications and should encourage a careful review of the antihypertensive therapy